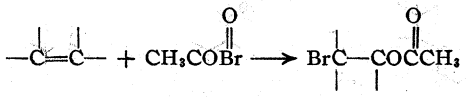
Steroidal Sapogenins. LI. Reaction of Steroidal Olefins with Acetyl Hypobromite[2a,b]

By Samuel G. Levine and Monroe E. Wall

Treatment of various steroidal olefins with acetyl hypobromite has yielded stable bromohydrin acetate adducts which, on saponification, produced the corresponding β-oxides. This method is compared with certain alternative routes with regard to scope, limitations and possible general advantages.

In the course of studies on the conversion of steroidal sapogenins to cortical hormones it was necessary to prepare a number of β-oxides from the corresponding steroidal olefin. Conventionally, hypobromous acid has been the reagent used for this purpose[3a-f] giving predominantly diaxial α-bromo-β-hydroxy compounds which yield the β-oxide on treatment with base. Several features of the hypobromous acid procedure seemed undesirable. This reaction is conducted in an acidic medium which, frequently, is incompatible with a spiroketal or other acid-labile functional grouping and at times other side reactions (*e.g.*, bromination) occur. Most important, in some cases, our wish to carry a stable intermediate through several stages before closure to the β-oxide was precluded by the lability of bromohydrins toward oxidation or even the mildest base treatment. For these reasons, we have explored the olefin addition of acetyl hypobromite as a one-step method of preparing steroidal bromohydrin *acetates* as our epoxide precursors.



1,2-Addition of an acyl hypohalite is thought to be the first step of the familiar Prévost oxidation[4] which, in cyclic olefins, leads to the corresponding *trans*-diol. The Winstein–Woodward modification leading to *cis*-diols has been similarly interpreted.[5] In these cases, the intermediate iodohydrin ester is not ordinarily isolated[6]; such addition products have been obtained, though, from a variety of aliphatic and monocyclic olefins.[4] However, the addition of acyl hypobromites to unsaturated polycyclic systems has received little attention.

1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

(2) (a) Presented in part at the 135th National A.C.S. Meeting, Boston, Mass., April 5–10, 1959; (b) Paper L, Walens and Wall, This Journal, **81**, in press (1959).

(3) (a) B. Ellis and V. Petrow, *J. Chem. Soc.*, 4417 (1956); (b) R. K. Callow and V. H. T. James, *ibid.*, 4739 (1956); (c) J. Fried and E. F. Sabo, This Journal, **75**, 2273 (1953); (d) B. Löken, S. Kaufmann, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 1738 (1956); (e) N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, *ibid.*, **78**, 5027 (1956); (f) E. P. Oliveto, C. Gerold and E. B. Hershberg, *ibid.*, **79**, 3596 (1957).

(4) C. V. Wilson, "Organic Reactions," Vol. IX, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 350.

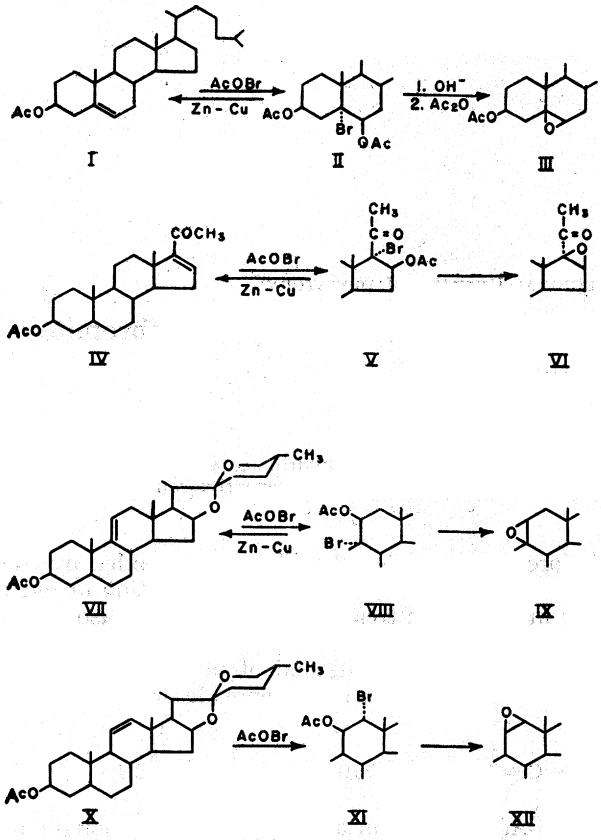
(5) R. B. Woodward and F. V. Brutcher, Jr., This Journal, **80**, 209 (1958).

(6) See, however, W. S. Knowles and Q. E. Thompson, *ibid.*, **79**, 3212 (1957).

The reagent was conveniently prepared by a modification of the procedure of Abbot and Arcus[7] which entails the addition of bromine to a cold suspension of silver acetate in carbon tetrachloride. The hypohalite solution thus prepared was assayed iodometrically and then added, in slight excess, to a cold solution of the steroidal olefin in carbon tetrachloride.

The non-acidic nature of the acetyl hypobromite reaction conditions is illustrated by the two-step conversion of cholesteryl tetrahydropyranyl ether to the corresponding 5,6-oxide without loss of the acid-sensitive protecting group.

When cholesteryl acetate (I) was treated in this manner, a mixture of bromohydrin acetates, principally II, was obtained. Saponification of this material followed by acetylation yielded cholesteryl acetate β-oxide[8] (III) as the major product, separable by crystallization from a smaller amount of the "α,β-oxide."[8]



Similar treatment of 3 β-acetoxy-5α-pregn-16-en-20-one (IV)[9] with acetyl hypobromite gave an addition product (V)[10] which was saponified to the corresponding 16β,17β-epoxy compound VI.

Two ring C unsaturated sapogenins were converted by this sequence into their corresponding β-oxides. Thus 3β-acetoxy-5α,22β,25D-spirost-9-(11)-en(VII)[11a] and 3β-acetoxy-5α,22β,25D-spirost-11-en(X)[11b] yielded the adducts VIII and XI, respectively, the latter compound obtainable only in resinous form. Saponification of XI followed by acetylation produced 3β-acetoxy-11β,12β-epoxy-5α,22β,25D-spirostane (XII)[12] identical with an authentic sample; saponification of VIII gave the hitherto unknown 3β-hydroxy-9β,11β-epoxy-5α,-22β,25D-spirostane (IX).[13]

An attempt was made to follow the progress of each of the above addition reactions by iodometric determination of unreacted acetyl hypobromite. However, in each case, the titer had reached a constant level (for 1 mole uptake) by the time the first two aliquots could be withdrawn. In contrast, it was found[10] that the addition of hypobromous acid to the olefinic linkage of IV, under the usual conditions[3a,b,c,e,f] required 5.5 hours for 80% completion.

In marked contrast to the above cases, methyl 3α-acetoxy-$\Delta^{9,11}$ cholenate was recovered mostly unchanged after treatment with acetyl hypobromite under the usual conditions. The particularly hindered nature of $\Delta^{9,11}$-cholenates toward addition reactions is also manifested in their inertness toward catalytic hydrogenation[14] and in the recovery of a preponderance of starting material from hypobromous acid addition conditions.[15]

We were also interested in testing the facility of iodohydrin acetate formation from two of the above-mentioned steroidal olefins. Accordingly, cholesteryl acetate (I) and the Δ^{16}-20-ketone IV were treated with iodine and silver acetate in glacial acetic acid using the procedure of Knowles and Thompson[6] and, in both cases, starting material was the only identifiable reaction product. These results are in accord with Shoppee's conclusion[16] that only disubstituted steroidal double bonds react easily under these conditions.[17]

Certain points of comparison may be made regarding the applicability of bromohydrin acetates as opposed to bromohydrins in a given reaction sequence. When the immediate conversion of a steroidal olefin to its β-oxide is intended, the over-all yields would seem to lie in the same range for the two methods; however, in cases where acid-catalyzed side reactions could occur, the acetyl hypobromite addition conditions (neutral and non-polar) are preferable. On the other hand, these adducts are clearly disadvantageous when oxidation to a

(7) D. C. Abbot and C. L. Arcus, *J. Chem. Soc.*, 1515 (1952).

(8) Pl. A. Plattner, Th. Petrzilka and W. Lang, *Helv. Chim. Acta*, **27**, 513 (1944).

(9) R. E. Marker, H. M. Crooks, Jr., R. B. Wagner and E. L. Wittbecker, THIS JOURNAL, **64**, 2089 (1942).

(10) The structure and reactions of this compound are the subject of the following paper.

(11) (a) R. Hirschmann, C. S Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3252 (1953); (b) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, *ibid.*, **76**, 4013 (1954).

(12) J. W. Cornforth, J. M. Osbond and G. H. Phillipps, *J. Chem. Soc.*, 907 (1954).

(13) The stereochemical course of these reactions can be rationalized in terms of an initial attack by $Br^{\oplus}$ on the less hindered (α) side of the steroidal double bond to give an intermediate bromonium ion which is then opened diaxially by β-attack of acetate ion. Saponification of the resulting bromohydrin acetate would then lead to β-oxides, as observed. This mechanism has been presented by Knowles and Thompson (ref. 6) in explanation of the mode of formation and saponification of an iodohydrin acetate.

(14) B. F. McKenzie, V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **175**, 249 (1948).

(15) E. M. Hicks, Jr., and E. S. Wallis, *ibid.*, **162**, 641 (1946).

(16) C. W Shoppee, D. N. Jones and G. H. R. Summers, *J. Chem. Soc.*, 3100 (1957).

(17) In a preliminary experiment, we have determined that acetyl hypochlorite [M. Anbar and I. Dostrovsky, *J. Chem. Soc.*, 1105 (1954)] adds to the conjugated ketone IV, giving a product m.p. 216–219°, $[\alpha]^{25}D$ +61.3°, whose infrared spectrum is very similar to that of V.

bromo-ketone is desired. A bromohydrin acetate would have particular advantage, though, when one is interested in carrying a *protected* olefin through one or more reaction steps prior to epoxide ring closure. In this regard we have found these adducts to be stable toward acid (2 *M* methanolic hydrogen chloride for 16 hours), mild alkali (aqueous alcohol at *p*H 9 for 16 hours or refluxing potassium acetate in acetone), and chromic acid oxidation. Indeed, since we have shown that by refluxing with zinc–copper in ethanol, the adducts III, V and VIII are efficiently reconverted to starting olefin, one may consider the addition reaction as an alternative (to bromine addition) olefin protective device.

Experimental[18]

Acetyl Hypobromite Reagent (Approx. 0.1 *M* in Carbon Tetrachloride).—Silver acetate (4.0 g.) was suspended in 160 ml. of carbon tetrachloride and stirred at 0° under anhydrous conditions. A solution of 1.00 ml. of bromine in 20 ml. of carbon tetrachloride was then added over 30 minutes with stirring and cooling. Stirring and cooling were continued for 90 minutes; by that time the red bromine color was no longer visible and the solution appeared light yellow-orange. Stirring was then stopped to allow the yellow precipitate (silver bromide) to settle. Portions of the clear supernatant liquid were withdrawn for iodometric titration and for use in the various addition reactions.

5α-Bromo-3β,6β-diacetoxycholestane (II).—Cholesteryl acetate (10.07 g.) was dissolved in 20 ml. of carbon tetrachloride and cooled to 0°. To it was added 250 ml. of 0.1 *M* acetyl hypobromite at 0°. After 5 minutes, the resulting solution was shaken with 5 ml. of cold 5% sodium bisulfite solution. The organic layer was then washed twice with water, dried over sodium sulfate, and concentrated to an oily residue which was crystallized from warm methanol yielding 10.55 g. (80%) of crude product, m.p. 78–88°, $[\alpha]^{25}D$ −58.0°; characteristic infrared bands at 1740 (broad, 3- and 6-acetate), 1240 (3-acetate), 1225 (6-acetate), 750 (halogen). Several crystallizations from methanol afforded a sample, m.p. 89–91°. *Anal.* Calcd. for $C_{31}H_{51}O_4Br$: Br, 14.1. Found: Br, 14.7.

17α-Bromo-3β,16β-diacetoxy-5α-pregnan-20-one (V).—3β-Acetoxy-5α-pregn-16-en-20-one (0.74 g.) was dissolved in 10.0 ml. of carbon tetrachloride and treated with 25.0 ml. of 0.095 *M* acetyl hypochlorite reagent in the manner described above. The product (0.725 g., 71%) was obtained as prisms from methanol, m.p. 202–206°. Two recrystallizations from methanol and one from hexane gave an analytical sample, m.p. 213.5–215.5°, $[\alpha]^{25}D$ +68.8°; characteristic infrared absorption bands at 1710 (20-ketone), 1730 (3-acetate), 1744 (16β-acetate), 1250 and 1230 (acetates), 760 (halogen). *Anal.* Calcd. for $C_{25}H_{37}O_5Br$: C, 60.35; H, 7.48. Found: C, 60.15; H, 7.66.

9α-Bromo-3β,11β-diacetoxy-5α,22β,25D-spirostane (VIII).—A solution of 0.60 g. of 3β-acetoxy-5α,22β,25D-spirost-9-(11)en in 25 ml. of carbon tetrachloride was cooled to 0° and treated with 20 ml. of 0.10 *M* acetyl hypobromite reagent as described for compound II. Following the usual work-up, the product was obtained as plates from methanol, 0.43 g. (56%), m.p. 170–175°, $[\alpha]D$ −19.8°; characteristic infrared bands at 1737 (broad, 3- and 11-acetate), 1230–1250 (3- and 11-acetates), 760 and 730 (halogen). *Anal.* Calcd. for $C_{31}H_{47}O_6Br$: Br, 13.4. Found: Br, 13.2.

12α-Bromo-3β,11β-diacetoxy-5α,22β,25D-spirostane (XI).—A solution of 0.45 of 3β-acetoxy-5α,22β,25D-spirost-11-en in 10 ml. of carbon tetrachloride was treated with 10.0 ml. of 0.11 *M* acetyl hypobromite reagent as described for compound II. After the usual work-up followed by filtration through a short column of Florisil,[18] the product was obtained as a viscous oil; characteristic infrared absorption bands at 1735 (broad, 3- and 11-acetates), 1245 (3-acetate), 1230 (11-acetate), 762 and 735 (halogen).

Cholesteryl-Acetate β-Oxide (III).—The bromodiacetate II (3.0 g.) was heated under reflux for one hour with 80 ml. of 5% methanolic sodium hydroxide. The solution was then cooled, neutralized with glacial acetic acid, concentrated to low volume at reduced pressure, and mixed with 100 ml. of water. After collecting, washing, and drying, the total crude product (2.2 g.) was acetylated with pyridine–acetic anhydride at 90° for 40 minutes. Following the usual work-up, the product was crystallized from methanol. Several fractional crystallizations from the same solvent yielded 0.8 g. (34%) of prisms, m.p. 111–113°, $[\alpha]^{25}D$ +1°, and 0.4 g. (17%) of plates, m.p. 102–110°, $[\alpha]D$ −17.3°; lit.[8] gives cholesteryl acetate β-oxide, m.p. 112–113°, $[\alpha]D$ −0.2°; cholesteryl acetate "α,β-oxide," m.p. 114–115°, $[\alpha]D$ −23.4°.

Preparation of Cholesteryl Oxide Tetrahydropyranyl Ether (as Stereoisomeric Mixture).—Cholesteryl tetrahydropyranyl ether[19] (0.40 g.) in 10 ml. of carbon tetrachloride was treated with 10 ml. of 0.11 *N* acetyl hypobromite reagent in the usual manner. The reaction solution was then washed with cold, dilute sodium bisulfite followed by water, dried over sodium sulfate, and concentrated to an oil. The residue was saponified with methanolic potassium hydroxide and the product crystallized from methanol to give 0.28 g. (68%) of wide melting (105–135°) blades. The infrared spectrum was devoid of absorption in the hydroxyl region. The material was not further separated or characterized.

16β,17β-Epoxy-3β-acetoxy-5α,17-iso-pregnan-20-one (VI).—17α-Bromo-3β,16β-diacetoxy-5α-pregnan-20-one (V) (0.15 g.) was heated under reflux for one hour with 10 ml. of methanol, 2 ml. of water and 0.25 g. of potassium carbonate. The solution was then concentrated at reduced pressure, diluted with water, and the product extracted with ether. The residue from the dried, concentrated ether extract was acetylated with acetic anhydride–pyridine at room temperature. Following the usual work-up the acetate was twice crystallized from methanol to yield 75 mg. (71%) of product, m.p. 158–159°, $[\alpha]^{25}D$ −64.2°; infrared spectrum: 1705 (20-ketone), 1735 (acetate), 860 and 900 (oxide?). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.04; H, 9.64.

9β,11β-Epoxy-3β-hydroxy-5α,22β,25D-spirostane (IX).—The bromodiacetate VIII (0.152 g.) was heated under reflux with 5.0 ml. of 4% methanolic potassium hydroxide for 90 minutes. Solvent was mostly removed at reduced pressure and the concentrate taken up in ether, washed and dried. Removal of solvent and crystallization of the residue from hexane gave 69 mg. (62%) of needle crystals, m.p. 174–176°, $[\alpha]^{25}D$ −13°. *Anal.* Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.09; H, 9.88.

The corresponding α-oxide[20] is reported to have m.p. 213–215°, $[\alpha]D$ −70°.

11β,12β-Epoxy-3β-acetoxy-5α,22β,25D-spirostane (XII).—Amorphous bromodiacetate XI (0.16 g.) was saponified by the above procedure and then acetylated with acetic anhydride and pyridine at room temperature. The mixture melting point and infrared spectrum of the product were identical with an authentic sample of the β-oxide XII, m.p. 200–206°.

Debromoacetoxylation of the Adducts II, V and VIII.—Zinc-copper couple was prepared according to the procedure of Elks, *et al.*[21]; 47 mg. of the bromodiacetate VIII was dissolved in 6.0 ml. of ethanol and heated with stirring and under reflux with zinc–copper (from 0.9 g. of zinc dust) for 3 hours. Solids were then removed by filtration through Super-cel[18] and the clear solution evaporated to dryness. The residue, in benzene solution, was washed with water, dried, and filtered through a short column of Florisil.[18] Crystallization of the concentrate from methanol afforded a halogen-free product (25 mg., 70%) identical in mixture melting point and infrared spectrum with 3β-acetoxy-5α-22β,25D-spirost-9(11)en, m.p. 204–207. Similar treatment of II and of V effected the regeneration of cholesteryl acetate (I) and of 3β-acetoxy-5α-pregn-16-en-20-one (IV), respectively.

(18) Infrared spectra were obtained in carbon disulfide solution, 10.0 g./liter. Optical rotations were measured in chloroform using a 2 decimeter tube, approximately 12.5 g./liter. We wish to thank C. S. Fenske and C. T. Leander for infrared data, S. Serota for optical rotation measurements, and Ruth B. Kelly for elemental analyses. Specification of brand names of materials used does not imply endorsement over other similar commercial products.

(19) W. G. Dauben and H. L. Bradlow, THIS JOURNAL, **74**, 559 (1952).

(20) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).

(21) J. Elks, G. H. Phillips, T. Walker and L. J. Wyman, *J. Chem. Soc.*, 4330 (1956).

Attempted Conversion of I and IV to their Iodohydrin Acetates.—Cholesteryl acetate (I) (0.240 g., 0.00056 mole) and 0.200 g. (0.00056 mole) of 3β-acetoxy-5α-pregn-16-en-20-one each were allowed to react with 0.101 g. of silver acetate and 0.148 g. of iodine in 1.8 ml. of glacial acetic acid and 0.6 ml. of chloroform according to the procedure of Knowles and Thompson.[6] The starting olefins were recovered in approximately 65% yield in both experiments. Resinous, halogenated material was also formed, in each case, which on treatment with base gave little indication (infrared spectrum) of epoxide formation.